REMARKS/ARGUMENTS

Claims 6 and 16 are canceled without prejudice or disclaimer. Therefore, claims 1-2, 10-11 and 20 are pending.

In response to the Examiner's comments under 35 USC § 112, first paragraph, claims 1 and 10 are amended to incorporate the subject matter of canceled claims 6 and 16, respectively. No new matter is added by this amendment.

The Examiner's comments are addressed in the order they were made below.

I. Formal Matters

The declaration was held to be defective for incorrectly stating the filing date of parent application 08/392,935. Accordingly, a new corrected declaration is herein attached.

II. Rejections Under 35 USC § 112, second paragraph.

Claim 11 was held to be indefinite for recitation of the term "carniosynostosis". In response, claim 11 is corrected to recite "heterotrophic cranial synostosis". Support for this amendment is found in the specification at paragraph [0008]. Accordingly, this rejection may now be withdrawn.

III. Rejections Under 35 USC § 112, first paragraph.

Claims 1, 2, 6, 10, 11, 16 and 20 were rejected on the basis that "no working examples directed to protein therapy of patients already suffering from FOP or any other BMP-related disorder are provided." The Examiner concedes that the specification "discloses that gene therapy with nucleic acids encoding noggin protected mice against ossification upon subsequent treatment with a BMP-4 implant" but states that "this working example does not speak to how a noggin *polypeptide* would affect a patient *already suffering from a bone disorder*" as recited in the claims (emphasis in the original, Office action dated 28 Nov 2006, pages 3-4, bridging paragraph). The Examiner's rejection is based on the quantity of experimentation required to determine how/when noggin should be administered to a patient already suffering from a BMP-related disorder, (2) lack of direction/guidance regarding the same, (3) the complex nature of the invention, (4)

contradictory state of the prior art, and (5) the scope of the claims with the exception of claim 20.

Applicants submit that the Examiner has failed to state a *prima facie* case for nonenablement.

In asserting a *prima facie* case for nonenablement in the face of Applicants' disclosure, which provides evidence of efficacy of the claimed treatment method in a mouse model, the Examiner must provide a rational explanation to doubt the veracity of Applicants' evidence for enablement. To state a *prima facie* case for nonenablement, the Examiner is burdened with establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants submit that the Examiner has not met this burden for the reasons stated below, including providing no rational basis to doubt the veracity of the specification's teachings of successful treatment of a BMP-related disorder by the claimed treatment method. Instead, the Examiner has substantially raised the patentability bar, essentially requiring, for purposes of enabling treatment claims, "working examples directed to protein therapy of patients already suffering from FOP or any other BMP-related disorder." Applicants respectfully submit that this standard is (1) legally incorrect, (2) arbitrary, and (3) insurmountable without providing results of a completed FDA-approved Stage III clinical study. Accordingly, Applicants submit that the Examiner's observations and remarks do not articulate a *prima facie* case for nonenablement of the pending claims. Since the Examiner's observations and remarks do not state a *prima facie* case for nonenablement, the rejections should not be applied to the pending claims and the pending claims should be allowed.

Assuming for the purposes of argument that the Examiner has stated a *prima facie* case for nonenablement, and that the nonenablement rejection might be applied to the amended claims, Applicants respectfully traverse the rejection.

The well-established test of enablement is whether the disclosure of the specification, when taken together with knowledge available in the pertinent art, enables one of ordinary skill in the pertinent art to make and use the claimed invention without undue experimentation. The teachings of the specification are to be considered in combination with knowledge available in the pertinent field as of the application's effective

filing date. The presence or absence of "working examples" is not, when taken alone, determinative of enablement. Contrary to the implications of the office action (pages 3-4), such working examples are not required (MPEP § 2164.02).

Initially, it is respectfully pointed out that the claims are amended to methods of using the human noggin ***protein*** (hNOG) of SEQ ID NO:2 or the hNOG△B2 mutant of SEQ ID NO:10.

Secondly, applicants respectfully point out the teaching and instructions provided in the specification for administration of hNOG at paragraph [0065], which describes subcutaneous administration of hNOG in a Matrigel™ implant in an animal model of BMP4-induced heterotopic ossification. The results are discussed in a later publication (Glaser *et al.* (2003) J Bone Joint Surgery 85A:2332-2342, at pages 2339-2340), which support the therapeutic use of hNoG and hNOG△B2 to treat BMP4-related conditions. The model reproduces characteristic stages of rhBMP-induced endochondral bone formation, and mimics all the states of heterotopic ossification seen during ectopic bone induction in at least one BMP-related disorder (*i.e.*, fibrodysplasia ossificans progressiva, or FOP). The claimed treatment method effectively treats the disorder, as disclosed in the specification and in the later publication (see, for example, Glaser *et al.*, at page 2335 cols. 1-2). Thus, the teachings of the specification contradict the Examiner's allegation that the working examples provided in the instant specification "do not speak to how a noggin polypeptide would affect a patient already suffering from a bone disorder".

Further, applicants respectfully submit that the Examiner is applying an inappropriately high standard of enablement. As stated in *In re Wands*, 8 USPQ 2d 1400 at 1401, enablement is not precluded by the necessity of some experimentation such as routine screening, as long as that experimentation is not undue. Applicants are not required to re-teach what is well-known to those skilled in the art; the specification preferably omits that which is well-known to those of skill in the art. MPEP 2164.05(a), citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Those in the field are aware of how to use protein therapeutics and how to determine the necessary formulations, doses,

frequency of administration, in order to achieve the therapeutic effect desired. These parameters are routinely determined for all protein therapeutics used or proposed to be used to treat human disease and are well within the level of skill of the art. Those of skill in the art are prepared to undertake the routine experimentation required to determine these parameters. Because the level of experimentation required to determine these parameters does not exceed a level the skilled person in the art is prepared to undertake, the claimed methods do not lack enablement. Further, there is no requirement that dosage disclosure is necessary for enablement. *In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51 (CCPA 1981) (dosage disclosure not required to enable prostaglandin analogs).

The invention is drawn to the treatment of a disease related to a bone morphogenic protein, by treating the disease with a recited composition that is an antagonist with respect to that bone morphogenic protein. Thus there is nothing unduly broad or unusual about the nature of the invention.

The claims are moderate in breadth. They are limited to treating a BMP-related disorder by administering a specifically recited and disclosed BMP antagonist or fragment thereof that is capable of acting as a BMP antagonist. Thus, the bone disorder is a disorder that is BMP-related and that can be treated with the recited BMP antagonist or fragment thereof. The BMP antagonist is specifically disclosed and recited in the claims (*i.e.*, human noggin, SEQ ID NO:2). The variant or fragment thereof must be capable of acting as a BMP antagonist, and Applicants describe such antagonists (*e.g.,* noggins in which the heparin-binding site is removed, *e.g.*, hNOGΔB2 (SEQ ID NO:10)). Thus, the specification teaches what functional feature of the recited antagonist must be maintained in any fragment thereof, and disclose fragments that lack certain functions but not the claimed function. The recited antagonist, and a fragment thereof, is shown to successfully treat a BMP-related disorder in a mouse model.

The state of the art is such that Applicants' teachings can be applied without undue experimentation. The level of skill in the art is high; once a person of ordinary skill reads and understands the specification, methods for treating BMP-related disorders with noggin as claimed can be practiced without undue experimentation. Applicants' disclosure provides the nexus between BMP activity, structure and function in a BMP antagonist, and treatment with noggin or a fragment thereof as a BMP antagonist. Applicants' specification

teaches a regimen for the antagonist in an *in vivo* mouse model (see, for example, paragraphs [0034] through [0036] and [0064] through 0065]), and that noggin mutants that comprise deletions (*e.g.*, including deletions in noggin's heparin-binding domain) can also effectively treat the mouse model by their activities as BMP antagonists.

Applicants respectfully disagree with the Examiner that the claims are "extremely broad" because they are not limited to a single specific BMP-related disorder treatable by the recited BMP antagonist, and because they do not recite all the effects that the recited BMP antagonist might have.

The specification discloses treatment of a specific BMP-related disorder in an animal model, and also discloses the efficacy of the claimed method as a method of antagonistic treatment with respect to BMP activity. The Examiner has provided no rational basis to doubt Applicants' disclosure that it is noggin's function as a BMP antagonist, not its function of binding to heparin sulfate, that forms the basis for its utility in treating a BMP-related disorder. There is no rational basis to assert that a person of ordinary skill would have any problem whatsoever in selecting the claimed treatment method once it is realized that an individual is suffering from a BMP-related disorder. Functional language in the claim, *i.e.*, treatment with the recited BMP ***antagonist***, makes it perfectly clear to a person of ordinary skill that the BMP-related disorder to be treated would be one that would benefit from treatment with a BMP ***antagonist***. Accordingly, Applicants submit that the claims are not "extremely broad" for the reasons recited by the Examiner.

Further, the Examiner's concerns regarding alleged unpredictability of the claims due to the biological functions of BMPs, arising out of the Examiner's reading of the Yamagita reference (Cytokine and Growth Factor Reviews 16:309-317), are misplaced. The Examiner has credited all the teachings of Yamagita that allegedly negate therapeutic activity, while at the same time discrediting the teachings and examples of the specification, without providing any rational basis for doing so. For example, the Examiner's rejection relies at least in part on Yamagita's speculation that noggin "may" induce increased bone density and bone formation rates, but ignores any teachings that support the efficacy of the claimed treatment method (see, *e.g.*, paragraph [0032] of the specification; see also Glaser *et al.* (2003) J Bone Joint Surgery 85-A/12:2332-2342).

Moreover, Applicants submit that they are not required to disclose or teach all side effects of a pharmacologically active agent in order to enable the pending claims. Applicants disclosed how to use the claimed antagonists in treatment of a BMP-related disorder by disclosing, *inter alia*, the function of the antagonist and its effective use *in vivo* in a mouse model of disease, and thus the claims are enabled.

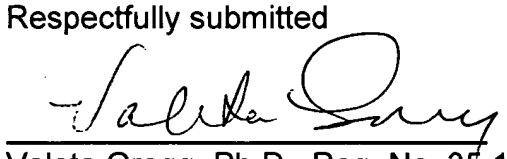
Conclusion

It is believed that this document is fully responsive to the Non-final Office Action mailed November 28, 2006. In light of the above, it is believed that the claims are in condition for allowance, and such action is respectfully urged.

Fees

It is believed that no fee is due with the submission of this response. In the event it is determined that a fee is due, the Commissioner is hereby authorized to charge Deposit Account Number 18-0650 for the amount of that fee.

Respectfully submitted



Valeta Gregg, Ph.D., Reg. No. 35,127
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 593-1077 (direct)